



How's my dosing? A one-step, math-free guide for comparing your clinic's maintenance immunotherapy doses to current practice parameter recommendations

Thomas J. Grier, PhD

Research and Development Laboratory, Greer Laboratories, Inc., Lenoir, North Carolina

ARTICLE INFO

Article history:

Received for publication December 9, 2011.

Received in revised form January 6, 2012.

Accepted for publication January 16, 2012.

ABSTRACT

Background: Immunotherapy dose recommendations for allergens specified in practice parameter updates have varied from version to version, and no convenient methods are available to incorporate dose changes or targets into maintenance vial formulations for patients.

Objectives: To compare the allergen immunotherapy dose recommendations published between 2003–2011, and to provide math-free dosing tables that translate dose targets for single or multiple extracts into maintenance vial compositions.

Methods: Dose recommendations obtained from immunotherapy practice parameters published in 2003, 2007 and 2011, plus a worksheet created in 2004, were tabulated and compared. Conversion tables were created based on the fixed mathematical relationships between extract concentrate strengths and maintenance immunotherapy dose targets. Considerations of stock mixes, glycerin levels, and allergen compatibilities were applied using two examples of common extract formulations.

Results: Changes to immunotherapy dose ranges for standardized extracts included adjustment of upper limits (short ragweed), lower limits (pasture grasses), or both (cat, dust mites, Bermuda grass). Dose ranges for non-standardized products have also been modified over time. Conversion tables specified the extract concentrate volumes or percentages required to deliver minimum, midrange and maximum recommended doses with 0.5 mL injection volumes.

Conclusions: These dosing guides, used in conjunction with cross-reactivity, compatibility and glycerin tolerance information, provide clinicians with a convenient and systematic method for determining the numbers and strengths of extracts that can be combined into treatment vials at various dose levels, and can facilitate optimization of maintenance immunotherapy mixtures for patients exhibiting a wide range of allergen sensitivities and specificities.

© 2012 American College of Allergy, Asthma & Immunology. Published by Elsevier Inc. All rights reserved.

Introduction

The administration of allergenic extracts at maintenance immunotherapy (IT) doses known to be both effective and safe is an essential practice in allergy clinics. Practice parameters for allergen IT have been published 3 times over the last 9 years, with each update containing different target dose levels or ranges for several allergens compared with previous and most recent versions.^{1–3} In addition, an IT worksheet distributed by the American Academy of Allergy, Asthma and Immunology (AAAAI) in 2004 included different dose ranges for most extract categories, compared with the corresponding values cited in the IT practice parameters published in 2003.⁴

In 2006, a simple, easy-to-use set of tables was created to define the volumes of extract concentrates required in IT mixtures to achieve the treatment doses cited in the practice parameters and to circumvent the need to perform multiple algebraic steps with each allergen contained in extract mixtures.⁵ These tables (based on the 2004 AAAAI worksheet doses and calculations using the common conservation of mass formula $V_1C_1 = V_2C_2$) identified the exact extract volumes or vial volume percentages corresponding to delivery of the minimum, midrange, and maximum dose levels within each specified range.

Because of the changes in IT dose recommendations reported in the subsequent 2007 and 2011 practice parameters, updates of these tables were needed.⁶ This report summarizes these changes and provides convenient, math-free dose conversion tables described in either specific extract volumes or percentages of total volumes to facilitate formulation of a wide variety of maintenance IT mixtures for patients receiving 0.5-mL injections. Use of volume percentage tables facilitates calculation of extract volumes for clin-

Reprints: Thomas J. Grier, PhD, Greer Laboratories, Inc., P.O. Box 800 Lenoir, NC 28645; E-mail address: tgrier@greerlabs.com.

Disclosures: The author is employed by Greer Laboratories, Inc. who provided financial support for this study.

Funding Sources: Greer Laboratories, Inc.

Table 1

Maintenance IT dose targets for standardized extracts reported in IT Practice Parameters and AAAAI Worksheet from 2003–2011

Extract category	Target IT doses or ranges			
	2003	2004	2007	2011
Short ragweed	6–24 AgE U (μ g) 1:30–1:100 w/v	6–12 AgE U (μg) 1:50–1:250 w/v	6–12 AgE U (μg)	6–12 AgE U (μ g)
Cat	2,000–3,000 BAU	2,000–3,000 BAU	1,000–4,000 BAU	1,000–4,000 BAU
Dust mites	600 AU ^a or 2,000 AU ^b	500–2,000 AU	500–2,000 AU	500–2,000 AU
Pasture grasses ^c	4,000 BAU	1,000–4,000 BAU	1,000–4,000 BAU	1,000–4,000 BAU
Bermuda grass	Not specified	Not specified	Not specified	300–1,500 BAU
Pollen	1:30–1:100 w/v	1:50–1:250 w/v	HTD	1:100–1:200 w/v
Fungi	1:50–1:100 w/v	1:50–1:250 w/v	HTD	HTD
Insects, animals	Not specified	Not specified	HTD	HTD
Dog AP	Not specified	Not specified	15 μg Can f 1	15 μ g Can f 1

Abbreviations: w/v, weight-to-volume ratio; AgE, Antigen E or Amb a 1; U, Unit; AU, Allergy Unit; BAU, Bioequivalent Allergy Unit; HTD, highest tolerated dose.

Changes from the previous publication are illustrated in bold type.

^a*D. pteronyssinus*.^b*D. farinae*.^cKentucky Blue/June, Meadow Fescue, Orchard, Perennial Rye, Redtop, Sweet Vernal, Timothy.

ics that formulate IT prescription vials at final volumes other than 5.0 mL and simplifies calculation of final glycerin concentrations in these mixtures. Revisions of these tables are required if injection volumes other than 0.5 mL are employed.

Methods

Recommended IT dose ranges

Maintenance IT dose ranges for licensed standardized and non-standardized allergenic extracts manufactured in the United States were obtained from the 2004 AAAAI Immunotherapy Prescription Worksheet and the 2003, 2007, and 2011 IT practice parameter updates.^{1–4} All doses described in these documents were based on a 0.5-mL injection volume. Nonstandardized extract dose targets were described in w/v terms for all extract types and concentrate strengths. Doses in protein nitrogen unit (PNU) strengths were not reported. Standardized short ragweed extracts were initially reported in both w/v and Amb a 1 (Antigen E, or AgE) units, and standardized Bermuda grass extracts were not included until the 2011 update. Selection of an appropriate dose range for Bermuda grass was complicated by the standardization of this product in a less sensitive study population than the 7 northern pasture grasses.³ For patients displaying comparable Bermuda and pasture grass sensitivities, doses proportional to their concentrate strengths were advised.⁵

Calculation of extract volumes and percentages

To calculate the volumes or percentages of each extract required to deliver specific maintenance IT doses, 3 variables must be defined: the total volume of the maintenance vial, the final extract concentrations in these vials, and the injection volumes. The practice parameter recommendations assume a 0.5 mL injection volume for both nonstandardized extracts in w/v strengths and standardized extracts in specific product units per milliliter, but lower (0.2–0.3 mL) and higher (0.7–1.0 mL) volumes are also used in some clinics. The initial dose tables from this author included data for 0.2-mL and 0.3-mL injections.⁵ In addition, although 5.0 mL vial volumes are commonly used in many clinics, some prefer lower (1.0–2.0 mL) or higher (6.0–10.0 mL) final volume formulations to meet the needs of their practice. The calculations in this report are based on the 2011 IT practice parameter dose ranges, 0.5 mL injection volumes, and either 5.0 mL or variable vial volumes to accommodate a wide variety of practice preferences. Adoption of a 0.5-mL injection volume facilitates dosing calculations for standardized products, in that the final concentration of each extract in a mixture is simply twice the numerical value of the final dose. For example, to administer 2,000 bioequivalent allergy units (BAU) of cat extract,

0.5 mL of a 4,000 BAU/mL solution is required. These values can be revised easily to address any desired IT vial volume–injection volume combination.

The volumes or percentages listed on the various conversion tables were calculated using either the conservation of mass formula $V_1C_1 = V_2C_2$ (V_1 and C_1 represent the initial volume and extract concentration, V_2 and C_2 the final values in the extract mixture), or dilution factors and fractional volumes relative to extract concentrates. Using the formula with a target dust mite extract dose of 2,000 AU, the formula becomes $V_1 \times 10,000 \text{ AU/mL} = 5.0 \text{ mL} \times 4,000 \text{ AU/mL}$, or $V_1 = 2.0 \text{ mL}$. Using the dilution factor approach, a 2.5-fold dilution of 10,000 AU/mL dust mite extract is required to prepare a 4,000 AU/mL solution, thus, 2.0 mL of this extract into a 5.0 mL final vial volume or 40% of the final formulation. (2.0 mL/5.0 mL \times 100).

Extract volumes and percentages were determined in this manner for extract doses at their lower limits (designated as Min in the tables), upper limits (Max), and mid-range values (Mid), and tabulated separately for formulations utilizing 5.0 mL or variable IT vial volumes.

Human subject participation was not required to perform these extract dose calculations; thus, this study was exempt from review by an institutional board or human subjects protection committee.

Results

Chronology of IT practice parameter dose recommendations

Maintenance IT doses published in the 2004 AAAAI IT worksheet and the 2003, 2007, and 2011 IT practice parameters are summarized in Tables 1 and 2. Changes from the previous publication are illustrated in bold type. The IT doses for standardized extracts were mostly consistent across the various updates (Table 1). The changes observed for these products included a reduced upper limit (short ragweed), reduced lower limit (pasture grasses), reduced lower plus increased upper limits (cat), and clarification of dose ranges for specific products (dust mite *Dermatophagoides* species). Bermuda grass doses were first reported in 2011 to differentiate IT recommendations for this subtropical species from those of the temperate pasture grasses. Nonstandardized extract dose recommendations were also modified across these documents (Table 1). Dose ranges were expanded and then narrowed (pollen), specified generically as the highest tolerated dose (HTD: fungi, insects), and reported at 1 dose based on a single study with an acetone-precipitated (AP) dog hair-dander extract.^{1–3}

Table 2
Extract volumes needed for 5.0 mL maintenance vials with 0.5 mL injection volume at minimum (min), mid-range (mid), and maximum (max) dose targets from 2011 IT Practice Parameters

Extract/concentrate strength		Volume of concentrate needed per vial (mL)		
Category	Concentrate	Min	Mid	Max
Pollens, fungi, insects	1:10 w/v	0.25	0.375	0.50
	1:20 w/v	0.50	0.75	1.00
	1:40 w/v	1.00	1.50	2.00
Short ragweed ^a	200 AgE U/mL	0.30	0.45	0.60
Cat	10,000 BAU/mL	1.00	2.50	4.00
Dog AP	1:100 w/v	NA	NA	1.00
Dog epithelia	1:10 w/v	0.25	0.375	0.50
	1:20 w/v	0.50	0.75	1.00
	30,000 AU/mL	0.17	0.42	0.67
Dust mites ^b	10,000 AU/mL	0.50	1.25	2.00
	100,000 BAU/mL	0.10	0.25	0.40
	10,000 BAU/mL	1.00	2.50	4.00
Bermuda grass	10,000 BAU/mL	0.30	0.90	1.50

Abbreviations: w/v, weight-to-volume ratio; AgE, Antigen E or Amb a 1; U, Unit; AU, Allergy Unit; BAU, Bioequivalent Allergy Unit; NA, Not applicable.

Minimum recommended dose was not specified for this extract category.

^aAlso applies to ragweed mix (short + giant) products at 1:20 w/v and approx. 100 AgE U/mL.

^bAlso applies to dust mite mix and pasture grass mix (eg, KORT, 7 grass) products at the same AU/mL or BAU/mL strengths.

IT formulation tables

Using the fixed mathematical relationships between extract concentrate strengths and final concentrations needed to deliver specific target doses, the volumes of extract concentrates to be added to 5.0 mL maintenance IT vials (or the percentages of these extracts in IT vials containing 5.0 mL or variable volumes) were determined to facilitate a convenient conversion of the 2011 IT practice parameter dose ranges for practical use, with no additional steps or repetitious calculations required. Extract concentrate volumes needed to deliver minimum, mid-range, and maximum doses are summarized in Table 2. These data expressed as percentages of the final vial volumes are shown in Table 3. The target dose range of 1:100 to 1:200 w/v for nonstandardized pollen extracts was also employed for fungal and insect extracts specified as HTD in the practice parameters, and for dog epithelia extracts that possess a different qualitative allergen profile compared with dog AP.⁷ For patients or geographic regions in which these doses are tolerated poorly, suitable reductions of these volumes or percentages, or use of similar volumes of the previous vial strength (10-fold dilution of maintenance concentrate), should be considered.

Using the Min, Mid, or Max columns of each table, the numbers and types of extracts that can be combined into IT vaccines are determined by adding the volumes or percentages from the col-

umns corresponding to the desired doses, up to the total vial contents (5.0 mL or 100%, respectively). For example, maintenance vials can contain up to ten 1:10 w/v extracts at maximum doses, or up to ten 1:20 w/v products at minimum doses (0.5 mL each or 10% of total volume).

Cross-reactive allergens contribute additive doses for many patients. Selection of extract mixtures within well-defined homologous groups may be preferred in some cases compared with single-species products from these groups.^{8–11} When stock mixes containing extracts from the same genus (ragweed mix, dust mite mix) or same tribe (pasture grass mixes) are used in place of a single-species representative, equivalent volumes and target doses are recommended (as noted in Tables 2 and 3).

When using stock mixes of unrelated or non-cross-reactive extracts, however, the allergen potencies are not additive but individualized and represent only a fraction of the total or labeled extract strength for these products. For example, a regional pollen mix composed of 6 unrelated tree species at a labeled (total) strength of 1:20 w/v actually contains each allergen at a final strength of 1:120 w/v. Volumes of these mixes added to IT prescriptions may need to be increased accordingly to achieve therapeutic doses. In some clinics, mixes such as these are used as maintenance IT concentrates without further extract additions or dilution.

Table 3
Extract volume percentages needed for 5.0 mL or variable volume maintenance vials with 0.5 mL injection volume at minimum (min), mid-range (mid), and maximum (max) dose targets from 2011 IT Practice Parameters

Extract/concentrate strength		% of Total vial volume		
Category	Concentrate	Min	Mid	Max
Pollens, fungi, insects	1:10 w/v	5	7.5	10
	1:20 w/v	10	15	20
	1:40 w/v	20	30	40
Short ragweed ^a	200 AgE U/mL	6	9	12
Cat	10,000 BAU/mL	20	50	80
Dog AP	1:100 w/v	NA	NA	20
Dog epithelia	1:10 w/v	5	7.5	10
	1:20 w/v	10	15	20
	30,000 AU/mL	3.4	8.4	13.4
Dust mites ^b	10,000 AU/mL	10	25	40
	100,000 BAU/mL	2	5	8
	10,000 BAU/mL	20	50	80
Bermuda grass	10,000 BAU/mL	6	18	30

Abbreviations: w/v, weight-to-volume ratio; AgE, Antigen E or Amb a 1; U, Unit; AU, Allergy Unit; BAU, Bioequivalent Allergy Unit; NA, not applicable. Minimum recommended dose was not specified for this extract category.

^aAlso applies to Ragweed mix (short + giant) products at 1:20 w/v and approx. 100 AgE U/mL.

^bAlso applies to dust mite mix and pasture grass mix (eg, KORT, 7 grass) products at the same AU/mL or BAU/mL strengths.

Table 4

Extract and glycerin content of 5.0 mL maintenance vial of example 1 IT mixture at minimum (min), mid-range (mid), and maximum (max) dose targets

Extract	Concentrate	Min (mL)	Mid (mL)	Max (mL)
Cottonwood	1:10 w/v, aqueous	0.25	0.375	0.50
Elm	1:10 w/v, aqueous	0.25	0.375	0.50
Maple	1:10 w/v, aqueous	0.25	0.375	0.50
Oak	1:10 w/v, aqueous	0.25	0.375	0.50
Pigweed	1:10 w/v, aqueous	0.25	0.375	0.50
Lamb's quarter	1:20 w/v, 50% glycerin	0.50	0.75	1.00
Short ragweed	200 AgE U/mL, 50% glycerin	0.30	0.45	0.60
Timothy	100,000 BAU/mL, 50% glycerin	0.10	0.25	0.40
Total allergen volume		2.15	3.325	4.50
Aqueous diluent volume needed		2.85	1.675	0.50
Glycerinated allergen volume		0.90	1.45	2.00
Final glycerin concentration		9.0%	14.5%	20.0%

Abbreviations: w/v, weight-to-volume ratio; AgE, Antigen E or Amb a 1; U, Unit; BAU, Bioequivalent Allergy Unit.

The final glycerin concentration of IT mixtures (in percentage) can be determined easily using either table. When using Table 2, add the volumes of all products supplied in 50% glycerin, then multiply by 10 (and add %). When using Table 3, add the percentages for all glycerinated items, then divide by 2. Glycerin levels above 20 to 25% may be difficult to tolerate for some patients; thus, monitoring the component and final glycerin levels in these mixtures is important to minimize pain or local reactions and promote adherence to treatment.¹²

Discussion

The establishment of appropriate dose ranges in IT mixtures remains a clinic-specific activity for many allergists in diverse geographic regions across the United States, owing in part to differences in exposures to provocative allergens and variable patient sensitivities to these allergens. Treatment guidelines contained in IT practice parameter updates include the quantities of standardized and nonstandardized extracts likely to produce successful therapeutic outcomes with most patients.^{1–3} Recognizing that these maintenance dose recommendations are derived from studies performed with both US and European extracts, and, in some cases, may not represent clinically relevant IT doses for certain allergic patients, is important.^{3,13} The appropriateness of these dosing guidelines with alum-precipitated depot extracts, when used in place of aqueous or glycerinated formulations of the same allergenic products, is also uncertain, and identification of effective IT doses and maintenance vial formulations for patients remains an individualized process.³ The objective of this report is to provide a precise conversion of 2011 IT practice parameter dose recommendations into practical extract volumes or vial percentages that can simplify calculations or facilitate mixing procedures in clinical settings. The data contained in this report apply strictly to the 2011 practice parameters, and, as inferred, are not necessarily applicable to all IT formulations and treatment regimens.

Comparisons of the maintenance doses used in allergy clinics with those reported in the practice parameters require several algebraic steps and a concentration-to-dose conversion based on the volume of injected vaccine. Multiple calculations are typically required to account for differences in injection volumes, extract concentrate strengths, or allergen mix formulations within a single or group practice.

The conversion tables provided in this summary were created to eliminate the need for clinicians or mixing technicians to perform these repetitious mathematical computations. Using these tables alone (no additional calculations required), allergy professionals can quickly and accurately determine the numbers and strengths of extracts that can be combined into a maintenance IT mixture to deliver doses at various levels within the 2011 IT practice parameter ranges, facilitating the selection of extract combinations and formulations that are most appropriate for their patients.

Preparation of optimal maintenance vial mixtures (with minimum numbers of separate vials and injections) at final glycerin concentrations below 20 to 25% requires a balance of extract dose targets, use of aqueous extract concentrates for some allergens, and specific product combinations (with associated glycerin levels) that possess favorable allergen stabilities and compatibilities under typical storage conditions. Two examples of IT mixtures incorporating these vial formulation considerations are provided in the following sections. For these examples, the general extract compatibility guideline recommending separate vials for protease-rich (fungal, insect) and low-protease (pollen, dust mite, dog) extracts was applied.^{1–3,10,11}

In Example 1, a total of 10 pollen allergens producing positive skin tests have been selected as candidates for IT. These allergens include 5 trees (box elder, cottonwood, elm, maple, oak), 2 grasses (Kentucky blue, timothy) and 3 weeds (lamb's quarter, pigweed, short ragweed).

First, examine the 10 allergens for established patterns of cross-reactivity. Among the 5 trees, box elder and maple are members of the same genus and are highly cross-reactive. Similarly, Kentucky blue and timothy belong to the same grass tribe and exhibit moderate to high levels of cross-reactivity in grass-sensitive patients.

Selection of a single product or a mix is influenced in part by the product strengths and formulations available. If box elder is provided only in 50% glycerin but maple is offered in both aqueous and glycerinated forms, aqueous maple extract may be a better selection. Pollen count differences among cross-reactive species in a clinic's geographic region also may help to identify relevant allergens for immunotherapy. If a maple-box elder mix is also available at the same aqueous strength, it can be used at the same volumes as the maple extract alone (remember that cross-reactivity produces additive doses in genetically related mixes). Both Kentucky blue and timothy are supplied in 50% glycerin at the identical Bioequivalent Allergy Unit/mL strengths. Either product or a grass mix containing these species (such as KOT: Kentucky blue-orchard-timothy, or KORT: Kentucky blue-orchard-redtop-timothy) can be selected. For this example, timothy alone will be used.

The 8 pollen extracts selected for the example 1 IT mixture are compatible (all low-protease products) and can be combined into a single maintenance vial. To prepare a 5.0-mL vial, product volumes from Table 2 are tabulated and examined for total extract volumes and glycerin content (Table 4). Mixtures at the minimum, mid-range, and maximum dose levels are also favorable with respect to glycerin content (final glycerin concentrations at or below 20%).

In example 2, a more complex combination of 21 diverse allergens is selected for IT, including 4 trees (cottonwood, elm, oak, poplar), 4 grasses (Kentucky blue/orchard/redtop/timothy mix), 4 weeds (cocklebur, nettle, short ragweed/giant ragweed mix), 2 dust mites (*Dermatophagoides farinae*/*Dermatophagoides pteronyssinus* mix), 3 animals (cat, dog AP, dog epithelia), 3 fungi (*Alternaria*

Table 5

Extract and glycerin content of 5.0 mL maintenance vials of example 2 IT mixtures at minimum (min), mid-range (mid), and maximum (max) dose targets

Extract	Concentrate	Min (mL)	Mid (mL)	Max (mL)
Cottonwood	1:10 w/v, aqueous	0.25	0.375	0.50
Elm	1:10 w/v, aqueous	0.25	0.375	0.50
Oak	1:10 w/v, aqueous	0.25	0.375	0.50
Nettle	1:10 w/v, aqueous	0.25	0.375	0.50
Dog epithelia	1:10 w/v, aqueous	0.25	0.375	0.50
Dog AP	1:100 w/v, 50% glycerin	1.00	1.00	1.00
Cocklebur	1:20 w/v, 50% glycerin	0.50	0.75	1.00
Ragweed mix	100 AgE U/mL, 50% glycerin	0.30	0.45	0.60
Dust mite mix	30,000 AU/mL, 50% glycerin	0.17	0.42	0.67
KORT grass mix	100,000 BAU/mL, 50% glycerin	0.10	0.25	0.40
Total allergen volume in vial 1		3.32	4.745	6.17 ^a
Aqueous diluent volume needed		1.68	0.255	NA
Glycerinated allergen volume in vial 1		2.07	2.87	3.67
Final glycerin concentration in vial 1		20.7%	28.7%	29.7%
Alternaria	1:20 w/v, aqueous	0.50	0.75	1.00
Aspergillus	1:10 w/v, aqueous	0.25	0.375	0.50
Penicillium	1:10 w/v, aqueous	0.25	0.375	0.50
German cockroach	1:20 w/v, 50% glycerin	0.50	0.75	1.00
Cat	10,000 BAU/mL, 50% glycerin	1.00	2.50	4.00
Total allergen volume in vial 2		2.50	4.75	7.00 ^b
Aqueous diluent volume needed		2.50	0.25	NA
Glycerinated allergen volume in vial 2		1.50	3.25	5.00
Final glycerin concentration in vial 2		15.0%	32.5%	35.7%

Abbreviations: w/v, weight-to-volume ratio; AgE, Antigen E or Amb a 1; U, Unit; AU, Allergy Unit; BAU, Bioequivalent Allergy Unit.

^aFinal extract doses are below target levels when total vial volumes exceed 5.0 mL, in proportion to overage volume.^bFinal extract doses are below target levels when total vial volumes exceed 5.0 mL, in proportion to overage volume.

alternata, *Aspergillus fumigatus*, *Penicillium chrysogenum/notatum*), and 1 insect (German cockroach). Cottonwoods and poplars are members of the same genus and exhibit strong cross-reactivities. Cottonwood was selected for this example. The remaining extracts, and extract mixes, which contain homologous allergens (KORT, ragweed, dust mites), are dosed independently. Dog extracts are also dosed separately because of the distinct qualitative and quantitative (major allergen) compositions of these products (dog AP: high Can f 1, low Can f 3; dog epithelia: low Can f 1, high Can f 3).

Pollen and dust mite extracts are placed in separate IT vials from the fungal and insect extracts because of their potential incompatibility. Cat extracts are stable when mixed with fungi or insects and can be added to either vial. This flexibility could circumvent the need for additional IT vials and injections in some cases.

The formulations of the two vials for example 2 are shown in Table 5. The glycerin content of the low-protease mixture ranged from 20.7% (Min) to 29.7% (Max), and the high-protease mixture contained glycerin levels from 15.0% (Min) to 35.7% (Max). Depending on the specific patient tolerances to these glycerin concentrations, one or all of these formulations may be feasible. In a recent report, elevated glycerin levels in IT injections (even as high as 50% glycerin present in commercial glycerinated extract concentrates) did not result in a significant increase in the incidence of small or large local reactions at the injection site.¹⁴

In these examples, allergens at the same dose levels were included in the extract volume and glycerin calculations for demonstration purposes only. With either example or actual clinic IT mixtures, combinations of extracts at varying dose levels within the practice parameter range are commonly used, and they provide flexible and favorable treatment options for many patients.

In summary, the dose conversion tables and vial formulation examples described in this report provide clinicians with a convenient and systematic method for formulation of maintenance IT mixtures in a manner consistent with current practice parameter dosing and vial preparation recommendations. This information simplifies the cumbersome and repetitive formula-based calculations used in allergy clinics for routine production of IT vial formulations, and can assist allergists optimizing treatment

and dosing regimens for patients exhibiting a wide variety of allergen sensitivities.

Acknowledgments

The authors thank Donna Rekherth, MS, FNP and Lisa Ellman-Grunther, MD for their helpful discussions and valuable contributions to this work.

References

- [1] Li JT, Lockey RF, Bernstein IL, Portnoy JM, Nicklas RA. Allergen immunotherapy: a practice parameter. *Ann Allergy Asthma Immunol.* 2003;90:1–40.
- [2] Cox LS, Li JT, Nelson H, Lockey R. Allergen immunotherapy: a practice parameter second update. *J Allergy Clin Immunol.* 2007;120:S25–S83.
- [3] Cox L, Nelson H, Lockey R et al. Allergen immunotherapy: a practice parameter third update. *J Allergy Clin Immunol.* 2011;127 (1 Suppl):S1–S55.
- [4] American Academy of Allergy, Asthma and Immunology Immunotherapy Prescription Worksheet. Accessed from www.aaaai.org in 2004, but is no longer available from this website. Dose ranges included in the AAAAI IT worksheet can be found in: Esch RE. Specific immunotherapy in the U.S.A.: General concepts and recent initiatives. *Arb Paul Ehrlich Inst Bundesamt Sera Impfstoffe Frankfurt A M.* 2003;94:17–23.
- [5] Grier TJ. How's my dosing? Comparing your clinic's maintenance immunotherapy doses to IT practice parameter recommendations in one convenient, math-free step. *Ann Allergy Asthma Immunol.* 2007;98 (1 Suppl):A105–A106 (abstract).
- [6] Grier TJ. How's my dosing 2.0: Comparison of 2003–2011 immunotherapy practice parameter maintenance dose recommendations and updated math-free formulation tables. *Ann Allergy Asthma Immunol.* 2011;107 (5 Suppl):A29 (abstr).
- [7] Grier TJ, LeFevre DM, Duncan EA, Esch RE. Stability and mixing compatibility of dog epithelia and dog dander allergens. *Ann Allergy Asthma Immunol.* 2009;103:411–417.
- [8] Weber RW. Guidelines for using pollen cross-reactivity in formulating allergen immunotherapy. *J Allergy Clin Immunol.* 2008;122:219–221.
- [9] Weber RW. Cross-reactivity of pollen allergens: impact on allergen immunotherapy. *Ann Allergy Asthma Immunol.* 2007;99:203–212.
- [10] Esch RE. Allergen immunotherapy: what can and cannot be mixed. *J Allergy Clin Immunol.* 2008;122:659–660.
- [11] Esch RE, Grier TJ. Allergen compatibilities in extract mixtures. *Immunol Allergy Clin North Am.* 2011;31:227–239.
- [12] Van Metre TE, Rosenberg GL, Vaswani SK, Ziegler SR, Adkinson NF. Pain and dermal reaction caused by injected glycerin in immunotherapy solutions. *J Allergy Clin Immunol.* 1996;97:1033–1039.
- [13] Larenas-Linnemann D, Esch R, Plunkett P, et al. Maintenance dosing for sublingual immunotherapy by prominent European allergen manufacturers expressed in bioequivalent allergy units. *Ann Allergy Asthma Immunol.* 2011;107:448–458.
- [14] Calabria CW, Coop CA, Tankersley MS. The GILL study: glycerin-induced local reactions in immunotherapy. *J Allergy Clin Immunol.* 2008;121:222–226.